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PAPER

H-bond relays in proton-coupled electron transfers. Oxidation of a phenol concerted with proton transport to a distal base through an OH relay

Cyrille Costentin, Marc Robert, Jean-Michel Savéant* and Cédric Tard

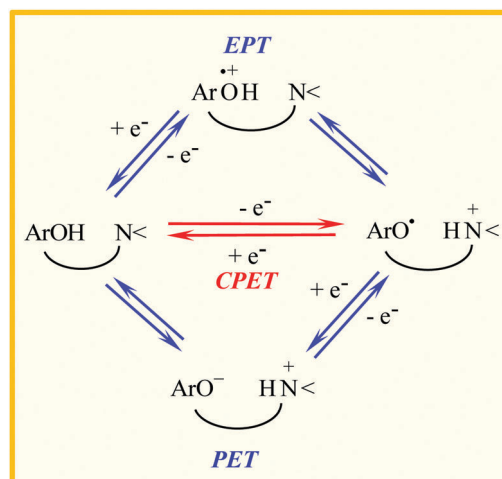
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Four molecules comprising a phenol moiety and a distal pyridine base connected by an intermediary H-bonding and an H-bonded alcohol group have been synthesized and their electrochemistry has been investigated by means of cyclic voltammetry. The molecules differ by the substituent at the alcohol functional carbon and by methyl groups on the pyridine. The reaction follows a concerted proton–electron transfer pathway as confirmed by the observation of a significant H/D kinetic isotope effect in all four cases. The standard rate constants characterizing each of the four compounds are analyzed in terms of reorganization energy and pre-exponential factor. Intramolecular and solvent reorganization energies appear as practically constant in the series, in which a previously investigated aminophenol is included, whereas significantly different pre-exponential factors are observed. That the latter, which is a measure of the efficiency of proton tunneling concerted with electron transfer, be substantially smaller with the H-bond relay molecules than with the aminophenol is related to the fact that two protons are moved in the first case instead of one in the second. Within the H-bond relay molecules, the pre-exponential factor varies with the substituent present at the alcohol functional carbon in the order $\text{CF}_3 > \text{H} > \text{CH}_3$, presumably as the result of a fine tuning of the balance between the H-bond accepting and H-bond donating properties of the central OH group. The kinetic H/D kinetic isotope effect increases accordingly in the same order.

1. Introduction

Long-distance electron transfer^{1,2} and long-distance proton transfer³ are important issues in a number of natural systems. Processes in which electron and proton transfers are coupled and involve different sites (PCET reactions) are currently attracting intense attention with particular emphasis on the possibility that the two steps be concerted giving rise to CPET (concerted proton–electron transfer) reactions as opposed to stepwise pathways in which proton transfer precedes (PET) or follows (EPT) electron transfer (Scheme 1).^{4–6} The occurrence of concerted processes requires a short distance between the group being oxidized and the proton acceptor (and *vice versa* for a reduction process), which usually but not necessarily involves the formation of a hydrogen-bond between the two groups as in an emblematic system such as the tyrosine–histidine couple in Photosystem II.⁷ The distances over which the proton may travel as the result of a CPET reaction are



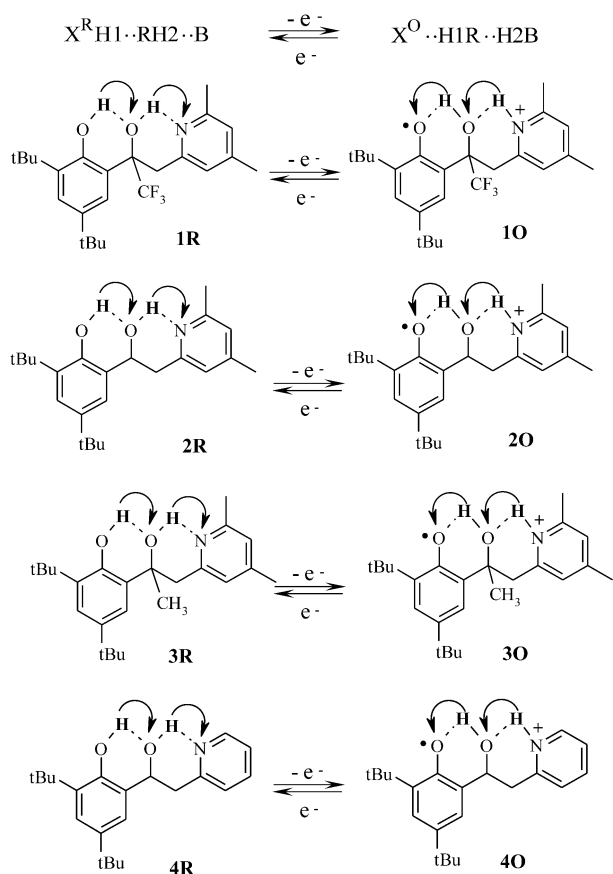
Scheme 1 PCET oxidation of a phenol ArOH bearing an attached proton acceptor, N<. Concerted (horizontal) and stepwise (oblique) pathways.

therefore limited to the rather small values that correspond to the formation of an H-bond in the starting molecule.

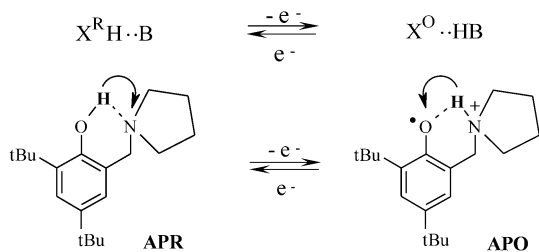
We have recently explored successfully the idea according to which this distance might be substantially increased by

Laboratoire d'Electrochimie Moléculaire, Unité Mixte de Recherche Université – CNRS No 7591, Université Paris Diderot, Bâtiment Lavoisier, 15 rue Jean de Baïf, 75205 Paris Cedex 13, France. E-mail: saveant@univ-paris-diderot.fr

H-bond Relay Molecules



Amino Phenol



Scheme 2 Molecules and reactions investigated in this study.¹⁵

inserting a hydrogen-bond relay between the group being oxidized and the distant proton acceptor as represented in Scheme 1. The relay is a group bearing an H atom able to accept an H-bond from the moiety being oxidized and, at the same time, to form an H-bond with the proton accepting group, without going through a protonated state in the course of the reaction. The molecule that served as example for this “H-bond train” is the one denoted **1R** in Scheme 2, which gives rise upon oxidation to the distal cation radical **1O**.⁸ There is some resemblance between such processes and proton transport in water. Even though the molecules in Scheme 2 do not retain all the properties of chains of water molecules engaged in a Grotthuss-type transport of a proton, the OH group in the molecules of Scheme 2 possesses the basic property of water molecules in that it is both a hydrogen-bond

acceptor and donor. We indeed note that, albeit investigated over decades, the mechanisms of proton conduction in water continue to be under active experimental and theoretical examination.^{9–14}

Based on the kinetic characteristics of the electrochemical oxidation of the molecules listed in Scheme 2, derived from their cyclic voltammetric responses in acetonitrile, we discuss in the following the mechanism of the H-bond relay in the double proton transfer triggered by the uptake of one electron by the electrode. Analysis of the parameters that govern the efficiency of the relay is grounded on the comparison between the characteristics of the four molecules between themselves and to the previously investigated aminophenol represented as the **APR**/**APO** couple in Scheme 2.^{16–18} Observation of the H/D kinetic isotope effect in the series will provide precious additional indications.

Discussing proton and electron transfers in a tribute to the celebration of John’s 75th Birthday is a particular pleasure in view of his own early and vigorous contributions to these issues.^{19,20}

2. Electrochemistry of the H-bond relay molecules

The cyclic voltammetric responses of the H-bond relay molecules listed in Scheme 2 are shown in Fig. 1. The traces display partial chemical reversibility, the response of **1** being almost completely reversible. The partial lack of reversibility is presumably due to deprotonation of the cation radical followed by further oxidation, possibly involving traces of residual bases in the reaction medium and father–son reactions in which the starting molecule would also play the role of a proton acceptor. A precise analysis of the nature and

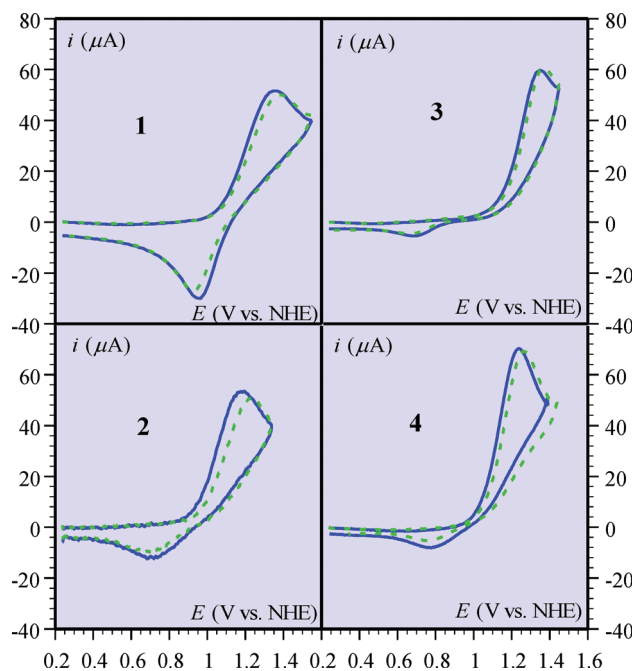


Fig. 1 Cyclic voltammetry of 1 mM of the molecules shown in Scheme 2 (number on each curve) in $\text{CH}_3\text{CN} + 0.1 \text{ M Bu}_4\text{NBF}_4$ at 2 V s^{-1} . Temp.: $23 \text{ }^\circ\text{C}$. Solid and dashed traces: in the presence of 1% CH_3OH or CD_3OD , respectively.

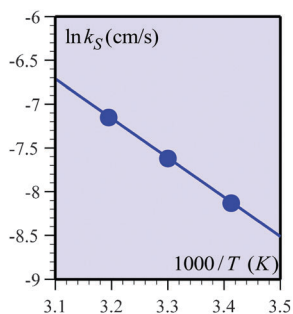


Fig. 2 Arrhenius plot for the oxidation of **1** in $\text{CH}_3\text{CN} + 0.1 \text{ M Bu}_4\text{NBF}_4$.

mechanism of these putative processes is beyond the scope of the present work. Nevertheless, the fact that all cyclic voltammetric traces show some chemical reversibility allows an approximate determination of the standard rate constant of the CPET reaction from the anodic-to-cathodic peak separation, the accuracy of which is sufficient for our purpose.

The concerted character of the reaction, already demonstrated for the **1R/1O** couple through $\text{p}K_{\text{A}}$ considerations and comparison with the oxidation of similar molecules where the pyridine group is absent,⁸ is confirmed by the significant H/D kinetic effect observed in the cyclic voltammograms for all four molecules (Fig. 2). With hydrogen as well as with deuterium, the standard rate constant may be derived by application of the Butler–Volmer law, with a 0.5 transfer coefficient.^{21,22}

$$\frac{i}{FS} = k_S \exp\left[\frac{F}{2RT}(E - E^0)\right] \left\{ [R] - \exp\left[-\frac{F}{RT}(E - E^0)\right] [O] \right\} \quad (1)$$

E^0 : standard potential of the redox couple; S : electrode surface area. $[R]$ and $[O]$: concentrations of reduced and oxidized forms at the electrode. k_S is the standard rate constant, *i.e.*, the rate constant for $E = E^0$. It is a measure of the intrinsic reactivity of the molecule toward oxidation.

Digital simulation of the anodic (E_{pa}) and cathodic (E_{pc}) peak potentials²³ then led to the k_S gathered in Table 1.

The cyclic voltammetry of **1** shown in Fig. 1 was repeated at two other temperatures in order to obtain a typical Arrhenius plot in the series. This is shown in Fig. 2, which represents the variation with temperature of the standard rate constant derived from the peak potentials in the same manner as described above, taking additionally into account the variation of 2% per degree of the diffusion coefficient revealed by the variation of the peak current.

Table 1 Electrochemistry of the H-bond relay molecules^a

Molecule	$E_{\text{pa,H}} (E_{\text{pa,D}})$	$E_{\text{pc,H}} (E_{\text{pc,D}})$	$\Delta E_{\text{p,H}} (\Delta E_{\text{p,D}})$	$E^0_{\text{H}} (E^0_{\text{D}})$	$k_{\text{S,H}} (k_{\text{S,D}})$	$\text{KIE}_{T=296\text{K}} = k_{\text{S,H}}/k_{\text{S,D}}$
1	1.350 (1.360)	0.960 (0.935)	0.390 (0.425)	1.150 (1.143)	9×10^{-4} (6.3×10^{-4})	1.45
2	1.180 (1.220)	0.720 (0.705)	0.460 (0.515)	0.944 (0.957)	4.5×10^{-4} (2.7×10^{-4})	1.70
3	1.340 (1.370)	0.700 (0.660)	0.640 (0.720)	1.016 (1.010)	8×10^{-5} (4×10^{-5})	2.00
4	1.240 (1.262)	0.780 (0.765)	0.460 (0.490)	1.005 (1.010)	4.5×10^{-4} (3.1×10^{-4})	1.45
AP ^{16,17}	—	—	—	0.85	8×10^{-3}	1.70

^a Potentials in V vs. NHE, the subscripts H and D indicate that the measurements have been carried out at 23 °C in the presence of 1% CH_3OH or CD_3OD , respectively. k_S in cm s^{-1} .

The Arrhenius plot may be described by the following equation.^{17,18}

$$\ln k_S = \ln Z^{\text{het}} - \frac{1}{4RT}(\lambda + 2F\phi_S + 4\Delta ZPE^{\ddagger} - 2\Delta ZPE) \quad (2)$$

where Z^{het} is the pre-exponential factor given by the intercept and the slope includes the total reorganization energy λ (internal reorganization λ_i + solvent reorganization λ_o), the potential difference between the solution and the reaction site, ϕ_S , and the zero-point energies in the transition state and in the initial state, ΔZPE^{\ddagger} and ΔZPE , respectively.

Eqn (2) is the result of an analysis of electrochemical CPET reactions that derives from a double application of the Born–Oppenheimer approximation to electrons, proton and heavy atoms of the system.^{17,18,24,25} The transition state is defined toward the heavy atom reaction coordinate by the intersection of two parabolae in the Marcus–Hush–Levich way (curves in Fig. 3).^{26–28} At the transition state, the dependence of the potential energy toward the proton coordinate q_{H} , or coordinates q_{H1} and q_{H2} , is depicted schematically in the upper insets of Fig. 3a and b, thus showing how electron transfer is concerted with proton tunneling. In the case of the H-bond relay molecules, the variation of the potential energy at the transition state is a surface, function of the two coordinates q_{H1} and q_{H2} , under which the two protons tunnel, whereas with the aminophenol it takes the form of a curve, function of the single coordinate q_{H} .

It is remarkable that the term $\lambda + 2F\phi_S + 4\Delta ZPE^{\ddagger} - 2\Delta ZPE$, = 1.550 eV, derived from the Arrhenius slope, is practically the same as for the aminophenol **AP** (1.544 eV¹⁸). In addition to this, DFT calculations of λ_i (see experimental section), giving the values reported in the second column of Table 2, point to a quasi-constancy of this parameter in the series, including **AP**.

Solvent reorganization, zero-point energies and the potential of the reaction site are also expected to be similar among these compounds. We may infer from these observations that the $\lambda + 2F\phi_S + 4\Delta ZPE^{\ddagger} - 2\Delta ZPE$ term should be practically constant in the whole series and close to 1.544 eV for the reactions involving proton transfer, and to 1.472 eV for deuteron transfer as obtained previously for the aminophenol. We may then obtain the values of Z^{het} for both the proton and deuteron transfer reactions (third column of Table 2) by application of eqn (2) using the above values of the $\lambda + 2F\phi_S + 4\Delta ZPE^{\ddagger} - 2\Delta ZPE$ term and the experimental values of k_S (Table 1).

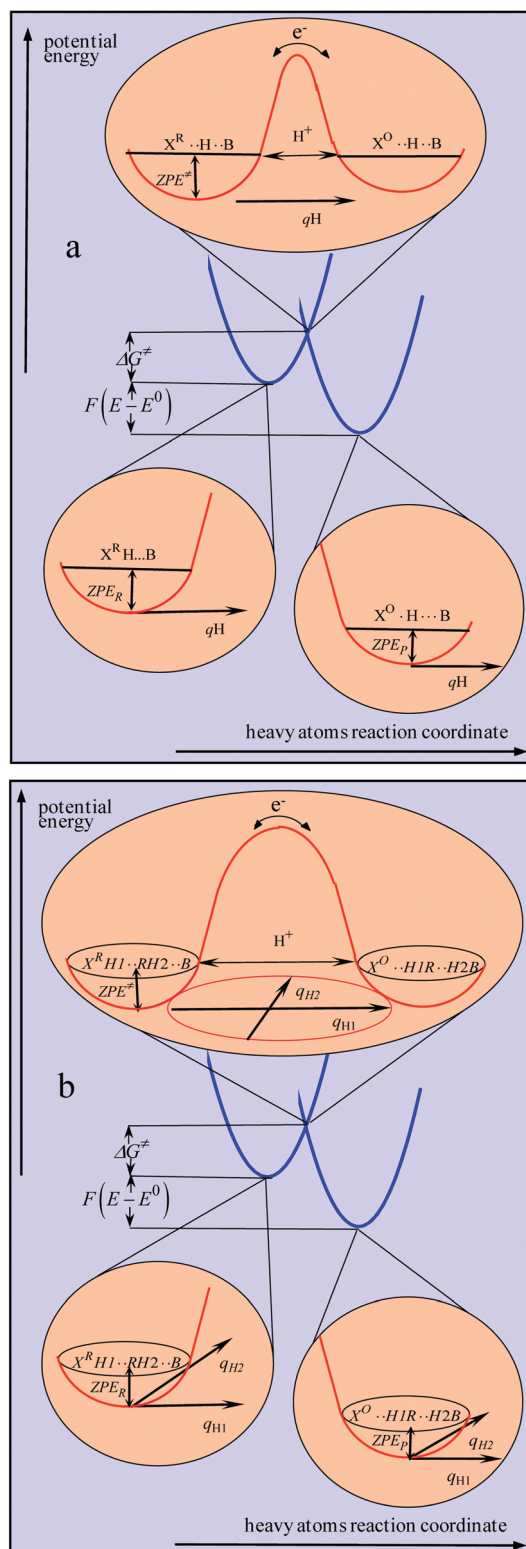


Fig. 3 Potential energy curves for the reorganization of the heavy atoms of the system, including solvent molecules (parabola) and for the proton displacement concerted with electron transfer (upper insets). In the aminophenol case (a) the dependence of potential energy toward the proton coordinate takes the form of a curve. In the H-bond relay case (b) it has the form of a surface. The symbols are defined in Scheme 2 and in the text.

As for the aminophenol,¹⁸ an estimate of the efficiency of proton tunneling is obtained by dividing the values thus obtained by the value of the pre-exponential factor that would have been obtained for a simple outersphere electron transfer under the same conditions ($Z_{\text{ref}} = 5.4 \times 10^4 \text{ cm s}^{-1}$). Even if this reference reaction is under the adiabatic regime, the low values obtained for all H-bond relay molecules (fourth column in Table 2) show that their CPET oxidation falls in the non-adiabatic regime in the whole series. A temperature-independent expression of the H/D kinetic isotope regime, simply designated by KIE can then be obtained as the ratio $Z_{\text{H}}^{\text{het}}/Z_{\text{D}}^{\text{het}}$ (fifth column in Table 2). As might have been expected, it is observed that the largest KIE corresponds to the lowest value of $Z_{\text{H}}^{\text{het}}/Z_{\text{ref}}$ (and $Z_{\text{D}}^{\text{het}}/Z_{\text{ref}}$), *i.e.* to the most difficult proton (deuteron) tunneling.

It thus appears that the intramolecular and solvent reorganization parameters are not the main factors that make the CPET oxidation of the four H-bond relay molecules intrinsically slower than the oxidation of the aminophenol in which a single proton is moved concertedly with electron transfer. Within the H-bond relay molecule series, in which two protons are moved concertedly with electron transfer, the observed variations of the standard rate constant from one compound to the other are similarly not related primarily to reorganization parameters.

The reason that makes CPET oxidation of the four H-bond relay molecules intrinsically slower than the oxidation of the aminophenol is thus essentially related to the magnitude of the pre-exponential factor as clearly appears in the third and fourth columns of Table 2. It is not too surprising that the efficiency of tunneling is less in the first case, where two protons are moved concertedly with electron transfer, than in the second where a single proton is transferred.

The variations of the pre-exponential factor within the H-bond relay series are likely to result from the influence of the substituents of the alcohol on the balance between the H-bond accepting and H-bond donating properties of the central OH group, inducing changes in the hydrogen potential energy surface at the transition state.

3. Experimental

Synthesis of the H-bond relay molecules

All manipulations were carried out using the standard Schlenk technique under an atmosphere of argon. THF was distilled over sodium/benzophenone. All other reagents were used as received. Microanalyses were obtained from the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer and were referenced to the resonances of the solvent used. Preparation of **1** has been published previously.⁸

Synthesis of 2. To a solution of 2,4,6-collidine (1.02 mL, 7.70 mmol) in anhydrous THF (50 mL) cooled at -78°C was added butyllithium (3.68 mL, 9.20 mmol, 2.0 M in cyclohexane). The orange mixture was left warming up to -30°C and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (1.50 g, 6.40 mmol) dissolved in THF (10 mL) was added to give a yellow solution.

Table 2 Analysis of the kinetics and mechanism of the H-bond-relayed CPET reaction^a

Molecule	λ_i^c	$Z_{\text{H}}^{\text{het}}$ ($Z_{\text{D}}^{\text{het}}$)	$Z_{\text{H}}^{\text{het}}/Z_{\text{ref}}^d$ ($Z_{\text{D}}^{\text{het}}/Z_{\text{ref}}^d$)	KIE = $Z_{\text{H}}^{\text{het}}/Z_{\text{D}}^{\text{het}}$
1	0.405 (0.386)	3539 (1220)	0.07 (0.02)	2.9
2	0.433	1770 (523)	0.03 (0.01)	3.4
3	0.420	315 (77)	0.006 (0.001)	4.1
4	0.443	1770 (600)	0.03 (0.01)	2.9
AP ^b	0.390 (0.410)	34580 (9985)	0.64 (0.18)	3.4

^a Energies in eV, pre-exponential factors in cm s^{-1} . ^b From ref. 18. ^c From the energy of the starting molecule in the geometry of the distal cation radical (see Scheme 1); in parentheses: from the energy of the distal cation radical in the geometry of the starting molecule. ^d $Z_{\text{ref}} = 5.4 \times 10^4 \text{ cm s}^{-1}$ is the value expected for a simple electron transfer reaction.¹⁸

The solution was then stirred for 2 h at RT. The reaction was quenched by the addition of ammonium chloride aqueous saturated solution (50 mL), and the product was extracted with diethyl ether, dried over MgSO_4 and purified by flash chromatography (cyclohexane/ethyl acetate 9/1) to give a colorless solid (1.54 g, 4.33 mmol, 67%). ¹H NMR (400 MHz, CDCl_3 , δ): 9.52 (1H, br), 8.00 (1H, br), 7.24 (2H, d, 2.2 Hz), 6.89 (1H, s), 6.87 (2H, d, 2.2 Hz), 6.80 (1H, s), 5.26 (1H, dd, 2.5 & 10.5 Hz), 3.45 (1H, dd, 10.5 & 15.7 Hz), 2.90 (1H, dd, 2.5 & 15.7 Hz), 2.51 (3H, s), 2.30 (3H, s), 1.43 (9H, s), 1.29 (9H, s). Anal. Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_2$: C, 77.70; H, 9.36; N, 3.94%. Found: C, 77.25; H, 9.29; N, 3.92%.

Synthesis of 3. To a solution of 2,4,6-collidine (0.45 mL, 3.43 mmol) in anhydrous THF (50 mL) cooled at -78°C was added butyllithium (1.60 mL, 4.00 mmol, 2.0 M in cyclohexane). The orange mixture was left warming up to -30°C and 1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)ethanone²⁹ (0.71 g, 2.86 mmol) dissolved in THF (10 mL) was added to give a yellow solution. The solution was then stirred for 2 h at RT. The reaction was quenched by the addition of ammonium chloride aqueous saturated solution (50 mL), and the product was extracted with diethyl ether, dried over MgSO_4 and purified by flash chromatography (cyclohexane/ethyl acetate 9/1) to give a colorless solid (0.54 g, 1.46 mmol, 51%). ¹H NMR (400 MHz, CDCl_3 , δ): 10.48 (1H, br), 9.07 (1H, br), 7.16 (2H, d, 2.5 Hz), 6.92 (2H, d, 2.5 Hz), 6.82 (2H, br), 3.54 (1H, d, 14.9 Hz), 2.96 (1H, d, 14.9 Hz), 2.43 (3H, s), 2.27 (3H, s), 1.59 (3H, s), 1.41 (9H, s), 1.25 (9H, s). Anal. Calcd for $\text{C}_{24}\text{H}_{35}\text{NO}_2$: C, 78.00; H, 9.55; N, 3.79%. Found: C, 77.83; H, 9.63; N, 3.50%.

Synthesis of 4. To a solution of 2-picoline (1.00 mL, 10.24 mmol) in anhydrous THF (25 mL) cooled at -78°C was added butyllithium (4.91 mL, 12.29 mmol, 2.5 M in cyclohexane). The orange mixture was left warming up to -30°C and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (2.00 g, 8.53 mmol) dissolved in THF (10 mL) was added to give a yellow solution. The solution was then stirred for 2 h at RT. The reaction was quenched by the addition of ammonium chloride aqueous saturated solution (50 mL), and the product was extracted with diethyl ether, dried over MgSO_4 and purified by flash chromatography (cyclohexane/ethyl acetate 9/1) to give a colorless solid (1.10 g, 3.36 mmol, 39%). ¹H NMR (400 MHz, CDCl_3 , δ): 9.32 (1H, br), 8.50 (1H, d, 4.4 Hz), 7.68 (1H, td, 1.8 & 7.9 Hz), 7.45 (1H, s), 7.24 (2H, d, 2.6 Hz), 6.88 (2H, d, 2.62 Hz), 6.80 (1H, s), 5.32 (1H, dd, 2.6 & 11.0 Hz), 3.56 (1H, dd, 11.0 & 16.2 Hz), 3.02

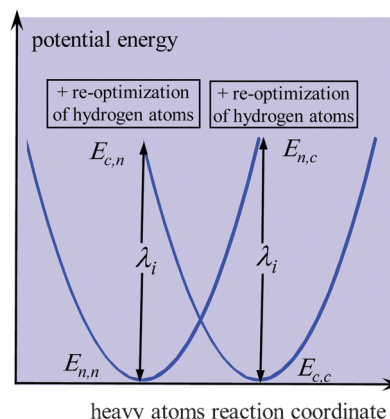
(1H, dd, 2.6 & 16.2 Hz), 1.44 (9H, s), 1.28 (9H, s). Anal. Calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_2$: C, 77.02; H, 8.93; N, 4.28%. Found: C, 76.88; H, 8.74; N, 4.56%.

Cyclic voltammetry

The working electrode was a 3 mm diameter glassy carbon (GC) electrode disk (Tokai) carefully polished and ultrasonically rinsed in absolute ethanol before use. The counter-electrode was a platinum wire and the reference electrode an aqueous SCE electrode. All experiments were carried out under argon at 23°C , the double-wall jacketed cell being thermostated by circulation of water. Acetonitrile (Fluka, >99.5%, stored on molecular sieves), the supporting electrolyte Bu_4NBF_4 (Fluka, puriss.), methanol and CD_3OD (Eurisco-top, 100%) were used as received. Cyclic voltammograms were obtained by use of a Metrohm AUTOLAB instrument with positive feedback compensation of the ohmic drop in all cases.

Quantum chemical calculations

All calculations were performed with the Gaussian 03 series of programs.³⁰ We used the B3LYP method with the 6-31G* basis set. To shorten the calculation time, computations were performed not on compounds **1** to **4** and **AP** but on simpler molecules where the *tert*-butyl groups were replaced by hydrogen atoms. The reorganization energies were calculated using a two-point method as depicted in Fig. 4. The geometries of both the neutral molecule and the cation radical were first fully optimized leading to the minimum energy values for both structures, respectively, denoted $E_{\text{n,n}}$ and $E_{\text{c,c}}$. Then the energy of the neutral molecule, $E_{\text{n,c}}$, was calculated in the geometry of

**Fig. 4** Calculation of the intramolecular reorganization energies, λ_i .

the cation radical regarding heavy atoms and the positions of the hydrogen atoms were re-optimized so as to get the minimal energy on the hydrogen potential energy surface. Similarly, for compound **1** the energy of the cation radical, $E_{n,r}$, was calculated in the geometry of the neutral molecule regarding heavy atoms while the positions of the hydrogen atoms were re-optimized. The reorganization energies are finally calculated from: $\lambda_i = E_{n,c} - E_{n,n}$ (and also $\lambda_i = E_{c,n} - E_{c,c}$ for compound **1** and **AP**).

4. Concluding remarks

In summary, electrochemical oxidation of the H-bond relay molecules depicted in Scheme 2, investigated by means of cyclic voltammetry, follows a concerted proton–electron transfer mechanism in all cases as confirmed by the observation of a significant H/D kinetic isotope effect. The standard rate constant, which characterizes the intrinsic reactivity of each molecule and its variation with temperature and with the replacement of the moving protons by deuterons may be analyzed in terms of reorganization energy (intramolecular and solvent reorganization) and pre-exponential factor. The first of these parameters appears as practically constant in the series, including a previously investigated aminophenol whereas significant differences are observed concerning the pre-exponential factor. The latter, which is a measure of the efficiency of proton tunneling concerted with electron transfer, is substantially smaller with the H-bond relay molecules than with the aminophenol as expected from the fact that two protons are moved in the first case instead of one in the second. Within the H-bond relay molecules, the pre-exponential factor varies with the substituent present at the alcohol functional carbon in the order $CF_3 > H > CH_3$, presumably as the result of a subtle balance between the H-bond accepting and H-bond donating properties of the central OH group. As expected, the kinetic H/D kinetic isotope effect increases in the same order.

Acknowledgements

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